Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 12-21, 26-32, 35-41, 46 and 48-71 are pending in the application, with claims 12, 19, 31, 40 and 46 being the independent claims. Claims 12, 14-17, 19, 21, 27, 32, 35-38, 48-50 and 53 have been amended to clarify the claimed invention. Claims 31 and 40 have been amended to specify what molecules are produced by the claimed method. New claims 54-71 have been added which depend from claims 31 and 40 and further specify what molecule is produced by the claimed method. Support for the new and amended claims can be found, *inter alia*, in the specification at paragraphs [0032], [0036], [0038]-[0039], [0058]-[0059], Figures 8-15 and in originally filed claims 1-11. Claims 22-25, 33, 34, 42-45 and 47 have been cancelled without prejudice to or disclaimer of the subject matter therein. In accordance with the Examiner's suggestion, claim 46 has been rewritten in independent form. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Elections/Restrictions

The Examiner has alleged that the following sequences recited in claims 23, 25, 45 and 47 are separate and distinct from each other: amino acids 50-87 of SEQ ID NO:18, amino acids 4-50 of SEQ ID NO:18, amino acids 86-176 of SEQ ID NO:18,

amino acids 176-262 of SEQ ID NO:18, amino acids 276-527 of SEQ ID NO:18, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16 and SEQ ID NO:17. Paper No. 0204, page 2. The Examiner has also alleged that a method for expressing each of these sequences is a separate and distinct invention. Paper No. 0204, page 2. Furthermore, the Examiner has alleged that the methods of expressing these proteins comprise steps which are not required for or present in the methods of expressing each of the others. Paper No. 0204, page 3. Finally, the Examiner has alleged that the operation, function and effects of these different methods are different and distinct from each other and that the end results of each of these methods differ. Paper No. 0204, page 3.

Applicants direct the discussion to SEQ ID NOs 10-17 and respectfully assert, contrary to the Examiner's indication, that these sequences fall within the scope of the claimed invention. SEQ ID NOs:10-17 correspond to variants of K2S. The specification depicts the secondary structure of these K2S variants in Figures 8-15. The predicted secondary structures show that these molecules fold in a similar manner and thus share common structural characteristics. Furthermore, each of these K2S variants includes the protease domain. *See* Specification, Figures 8-15. The protease domain, which contains the catalytic site of the molecule, is also responsible for converting plasminogen to plasmin, which is important for the homeostasis of fibrin formation and clot dissolution. *See* Manosroi *et al.*, *Appl. Env. Microbiol.* *67*:2657-2664 (2001) (cited as Document AT14 in the IDS filed August 20, 2002). Thus, the K2S variants described above share common functional characteristics, in addition to their common structural characteristics. Because these K2S variants fold similarly, and contain the same protease domain which

would allow them to function similarly, Applicants assert that a method for expressing these sequences, the steps required for the method, and the operation, function and effect of the method would be the same. Accordingly, Applicants assert that SEQ ID NOs:10-17 fall within the scope of the claimed genus.

Applicants note that claims 31 and 40 recite K2S variant. Claims 53-71, which depend from either claim 31 or 40 further specify which K2S variant is produced by the method. Applicants point out that the sequences specified in claims 31, 40 and 53-71 (SEQ ID NOs 10, 11, 12, 13, 14, 15, 16 or 17) correspond to those which encode the K2S domain of tPA, or variants of the K2S domain. Sequences corresponding to other domains of tPA (amino acids 50-87 of SEQ ID NO:18; amino acids 4-50 of SEQ ID NO:18; amino acids 86-176 of SEQ ID NO:18; amino acids 176-262 of SEQ ID NO:18; amino acids 276-527 of SEQ ID NO:18) which do not share the same secondary structure as SEQ ID NOs 10-17, are not recited in the currently pending claims. Applicants also refer the Examiner to the § 112, first paragraph, written description section below, for a further discussion of SEQ ID NOs 10-17.

Based on the arguments above, Applicants assert that the K2S variants corresponding to SEQ ID NOs:10-17 fall within the scope of the claimed genus. Thus, Applicants respectfully request that claims 31 and 40, and all pending claims depending from claims 31 and 40 be reconsidered and examined.

Provisional Double Patenting Rejection

The Examiner has provisionally rejected claims 31-33, 39, 52 and 53 under the judicially created doctrine of obviousness-type double patenting over claims 1-6 and 8-10 of copending Appl. No. 09/987,455. Paper No. 0204, pages 4-5.

According to § 804(I)(B) of the Manual of Patent Examining Procedure (M.P.E.P.), when provisional double patenting issues are raised in copending applications, "[i]f the 'provisional' double patenting rejections in both applications are the only rejections remaining in those applications, the examiner should then withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent. The examiner should maintain the double patenting rejection in the other application as a 'provisional' double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent."

Applicants will appropriately address the double patenting rejection in the event it is converted to an actual double patenting rejection pursuant to MPEP § 804(I)(B).

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 31-33, 39, 52 and 53 under 35 U.S.C. § 102(b) as allegedly being anticipated by Georgiou, *et al.* (U.S. Patent No. 6,027,888) ("Georgiou"). Paper No. 0204, page 6.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). MPEP § 2131.

Applicants have amended independent claim 31 so that the vector comprises DNA encoding a peptide selected from the group consisting of SEGN (SEQ ID NO:2) and SEGNSD (SEQ ID NO:3).

Pending claim 31 and claims 32-33, 39, 52 and 53 which depend from claim 31 are thus directed to a method for the production of an heterologous protein where the vector expressing the heterologous protein comprises the sequence encoding either SEGN or SEGNSD. Georgiou does not disclose a peptide which comprises SEGN or SEGNSD. Therefore, claims 31-33, 39, 52 and 53 are not anticipated by Georgiou. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claims 12-22, 24, 26-44 and 48-53 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Paper No. 0204, page 7. The Examiner has alleged that the claims are drawn to a method of expressing any heterologous protein, a tissue plasminogen activator or a fragment thereof. Paper No. 0204, page 7. The Examiner alleges that the claims are drawn to broad genuses of polypeptide for which no structure-function relationship has been described. Paper No. 0204, page 7. The Examiner further alleges that these genus claims encompass a wide array of molecules. Paper No. 0204, page 7.

Applicants respectfully disagree with the Examiner's characterization of the claims and will address the rejection with respect to heterologous protein and tissue plasminogen activator or K2S separately below.

The test for written description requirement is whether one skilled in the art can reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02.

Heterologous Protein

With respect to the method in claims 12-22, 24, 26-44 and 48-53, Applicants emphasize that the claims are directed to a method for the production of recombinant heterologous protein where the protein is *secreted extracellularly as an active protein.* Thus, the invention of these claims is not directed to heterologous protein, *per se*, but to an extracellular secretion method whereby one skilled in the art can recover a heterologous protein as an active protein. The present invention of these claims accomplishes this method for secreting heterologous protein as an active protein by utilizing a vector which comprises both the OmpA signal peptide and either a peptide encoding SEGN or SEGNSD. Where prior art methods have failed (*see* Specification, paragraphs [0006]-[0011]), Applicants have performed the method of these claims and achieved expression and secretion into the culture medium of active protein at a higher than expected fraction. *See* Specification, paragraph [0032].

Experiments described in the specification support this statement. For example, the specification at paragraph [0103] notes that when recombinant K2S is expressed in *E. coli* cells, 68% of the recombinant K2S protein can be directly isolated from the culture supernatant with only 32% of the recombinant K2S secreted into the periplasm.

Thus, Applicants have conveyed with reasonable clarity to one skilled in the art that they were in possession of the claimed invention as the specification adequately

describes a method to express heterologous protein in *E. coli* in order that the protein is secreted as an active protein into the culture medium. The Examiner has provided no evidence or rationale to indicate that one skilled in the art could not use the claimed invention to express other heterologous proteins in prokaryotic host cells in order that they are secreted into the culture medium in an active state.

In addition, the present invention describes other proteins which would be useful in the claimed method. For example, at paragraph [0041], the specification describes other heterologous proteins which could be expressed and secreted, such as insulin, insulin-like growth factor, cytokines, *e.g.* interleukins such as IL-1 through IL-18, interferon (IFN) alpha, IFN beta, IFN gamma, IFN omega or IFN tau, tumor necrosis factor (TNF) alpha and TNF beta, TRAIL, G-CSF, GM-CSF, M-CSF, MCP-1 and VEGF. Furthermore, the specification describes how the method according to the invention can be advantageously used for production of antibodies or fragments thereof. *See* Specification, paragraph [0042].

Applicants' method thus is directed to secreting a heterologous protein extracellularly as an active protein. Based on the disclosure in the specification, Applicants have conveyed with reasonable clarity to one skilled in the art that they were in possession of the claimed invention and that the claimed method is adequately described. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

K2S variant

Applicants point out that the Federal Circuit stated in *Univ. of Calif. v. Eli Lilly & Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997), that:

> A description of a genus of cDNAs may be achieved by means of a recitation of [1] *a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus* or [2]or a recitation of *structural features common to the members of the genus*, which features constitute a substantial portion of the genus....We will not speculate in what other ways a broad genus of genetic material may be properly described . . . .

Univ. of Calif., 43 U.S.P.Q.2d at 1406 (emphasis added).

Thus, the Federal Circuit has stated that the written description requirement for a claim directed to a genus of cDNAs may be satisfied by providing the sequences of a representative number of cDNAs which fall within the scope of the genus or by providing a recitation of structural features which are common to a substantial portion of the members of the genus. *See* Univ. of Calif., 43 U.S.P.Q.2d at 1406. Thus, in order to fall within the scope of the genus, the DNA sequence must have specific functional or structural characteristics.

Contrary to the Examiner's position, the specification discloses a representative number of cDNAs defined by nucleotide sequence, which fall within the scope of the genus and discloses that these representative sequences share common structural and functional features.

For example, the specification describes the sequences of K2S variants. These variants of K2S are described as: 1) amino acids 174-527 (SEQ ID NO:10); 2) amino acids 197-527 (SEQ ID NO:11); 3) amino acids 193-527, modified to include the amino acid sequence SEGN at the N-terminus (SEQ ID NO:12); 3) amino acids 193-527, modified to change the Cys at position 261 to a Ser (SEQ ID NO:13); 4) amino acids 191-527, modified to change the Cys at position 261 to a Ser (SEQ ID NO:13); 5) amino acids 220-527 (SEQ ID NO:16); and 6) amino acids 260-527 (SEQ ID NO:17). *See* Specification, paragraphs [0021]-[0029].

The specification also depicts the secondary structure of these K2S variants in Figures 8-15. The predicted secondary structures show that these molecules fold in a similar manner and thus share common structural characteristics. For example, the K2S molecule represented in Figure 11 where the Cys at position 261 is changed to a Ser, shares the same predicted secondary structure, particularly with respect to the protease domain, as the corresponding wild-type K2S structure shown in Figure 9. Similarly, other variants of K2S shown in Figures 8, 10, and 12-15 also form similar secondary structures as that of the wild-type K2S molecule. *See* Specification, Figures 8-15.

Each of the K2S variants shown in Figures 8-15, as well as wild-type tPA, includes the protease domain. The protease domain contains the catalytic site of the molecule at its C-terminus. *See* Manosroi *et al.*, *Appl. Env. Microbiol. 67*:2657-2664 (2001). The protease domain is also responsible for converting plasminogen to plasmin, which is important for the homeostasis of fibrin formation and clot dissolution. *See id.* Thus, not only do the K2S variants described above share common structural

characteristics as shown by their predicted secondary structures, they also all possess the same functional domain and thus all share common functional characteristics.

Thus, Applicants have disclosed a representative number of species, corresponding to variants of K2S, which fall within the scope of the genus of the claimed invention. Applicants have also shown these variants of K2S share common structural and functional characteristics. Thus, Applicants have conveyed with reasonable clarity to one skilled in the art that they were in possession of the claimed invention. Accordingly, Applicants assert that the written description requirement is satisfied and respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Applicants note that amended claims 31 and 40 recite K2S variant. Claims 53-71, which depend from either 31 or 40, recite the K2S variants corresponding to SEQ ID NOs 10-17. As described above, these sequences all share common structural and functional characteristics. Applicants note, as described above in the Elections/Restrictions Section, that SEQ ID NOs 10-17 were cited in previously pending claims 25 and 47 which the Examiner has alleged are directed to an invention independent and distinct from that originally claimed. Paper No. 0204, page 2. Applicants respectfully disagree with this characterization. Based on the arguments presented above, Applicants respectfully assert that the sequences recited in previously pending claims 25 and 47, and now in pending claims 31, 40 and 53-71 fall within the scope of the claimed invention.

Allowable Subject Matter

The Examiner has objected to claim 46, but has indicated that claim 46 would be allowable if rewritten in independent form. Paper No. 0204, page 9. In accordance with the Examiner's suggestion, Applicants have rewritten claim 46 in independent form. Accordingly, Applicants respectfully request that this objection be withdrawn.

Other Matters

Applicants thank the Examiner for considering SEQ ID NO:2 and SEQ ID NO:4 together with SEQ ID NO:5.

Copending Applications

Applicants refer the Examiner to Office Actions issued during prosecution of copending Appl. No. 09/987,455 (cited in the IDS submitted on August 20, 2002 as document AR18). Applicants would like to make the Examiner aware of a Final Office Action issued on May 4, 2004 for copending Appl. No. 09/987,455, subsequent to the issuance of the Final Office Action in the present application on March 9, 2004.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Michael A. Cimbala
Reg No 33851

for Eric K. Steffe
Attorney for Applicants
Registration No. 36,688

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600